

DERMATOLOGY OF TOMORROW: SOME AREAS FOR DERMATOLOGIC RESEARCH*

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In recent discussions, dermatologists have expressed some anxiety and misgivings about the future of dermatology as a specialty. There is a fear this discipline may become extinct through absorption into the larger body of medicine and science. Now that the purely descriptive phase of our art is almost past us, is there anything further to justify our distinction? Specifics, antibiotics, the newer steroids and such have already simplified the principles of therapy to where the partial expert can deal effectively with diseases whose care he formerly hesitated to enter upon. Does that mean there is little left for us to do or justify setting us apart as dermatologists? The evidence all about us answers overwhelmingly in the negative. Our trail is not at an end, but changing its direction; in fact, it is marching up several new avenues at once. I propose in this paper to sketch a rough map to highlight several guideposts to the newer and, as yet, lightly traveled foot paths.

Our predecessors and the old masters of our calling did well during the little more than past century to amass and organize the body of information at our disposal. Maybe the nuggets were lying near the surface and could be gathered up by simple strip mining. In the future, we shall need to dig more deeply to find treasure, but to do this some preparation is needed to work the necessary tools. How often do younger men ask for suggestions and guidance to investigative work, but how relatively seldom are they equipped by background and skills to undertake the attack on the host of matters awaiting to be done?

Anyone familiar with the problems of medical education will hesitate before advocating prolonging our course of preparation or adding to the number of disciplines necessary to train more than a routine dermatologist. Nevertheless, if we hold to the thesis that to show convincing vitality we must contribute something new, to do this we must meet an expanding technology. I am sure our ingenuity will find the means to rearrange specializing curricula to permit our students to acquire one or more investigative skills. The number of dermatologists in America so equipped continues to grow. Da Vinci was unique in knowing how to do everything well, and Unna astonished by his broad capabilities, but the rest of us must content ourselves with but one or two technical proficiencies. This is not to say that men of broad training will not continue to be invaluable as liaisons to visualize and integrate the work of men who plow narrow fields deeply.

Both epochal strides and the gradual pushing back of barriers will continue to be made by the genius or isolated worker, but the bulk of study, the sure prodding advance, will continue, as in the recent past, to come from the teamwork found

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only in centers of teaching and learning. The number of departments of dermatology equipped by personnel, organization and means to do investigative work is impressive and growing. There is heartening satisfaction to compare the number of men prepared to carry out technical studies with their number 20 years ago.

Has the art and science of psychology and personnel management advanced far enough to be of use to us in determining who shall be our future dermatologists? Do we know enough to predict which few is apt to be attracted to clinical or laboratory investigation? I believe the time is ripe for inquiries and answers. It will be of tremendous significance to know if appreciation of form, as shown by ability to draw or sculpt well, makes for keener discernment of cutaneous eruptions. Does ability to fit a word into multiple pictures and situations parallel capacity to conjure up possibilities or probabilities to go with a given rash? Does the non-conformist tend to develop more original ideas? Can curiosity in an individual be observed and measured, and does it augur a bent toward scientific inquiry? Such questions and many others await an answer by us working with colleague-experts in appropriate fields.

Heads of departments have large tasks and responsibilities to gather together members of diverse interests and pursuits integrated for their communal problems and transactions. All must be taught early the need and how to use the library without which most work is blind and isolated and apt to be sterile. On the other hand, some young men seem to bog down too far within the library, finding the enthroned past there to act as a brake or deterrent to activity in the laboratory or clinic. They must be encouraged to be doing, for trials resulting in failure often teach and provoke thought and lead finally to more positive attacks. Passivity throttles investigation but action soon becomes a habit.

American scientists have been called, "birds of prey", "scavengers" and "opportunists" because of their habit of appropriating and applying to practical ends the fundamental investigations of the Europeans. It has been asked, "What would Americans do with their mills without the grist from abroad?" I believe the non-prejudiced will find all about him here within our shores an awakening of the conscience to repay what we owe the common till of fundamental ideas and work. There is a newer emulation and assiduous application to the fundamental preparation and concern of the scholar. How common among us today is admiration of the classical simplicity of the work of such masters as Thomas Lewis, based on an unusual breadth and digestion of knowledge!

The wise head of department will guide his men according to their individual temperaments and bents and not force them into a mold convenient to immediate needs or even long term plans, no matter how important. Some of us are opportunists, plucking the rose along the wayside here and there, never reluctant to be distracted by some lesser crop springing up unexpectedly. The great Paul Ehrlich was such a one. Others among us have the fixity of view and determination of purpose to continue toward a goal no matter how discouragingly few might be the interim rewards.

As I see our future development, we must avoid the short-cut, convenient, though slavish dependence on outside experts. If we are to be free and respected,

every one of us must be, besides a competent dermatologist, familiar with auxiliary disciplines. The latter will be in the accepted fields as we have known them, anatomy and pathology, gross and microscopic, biochemistry and pharmacology, bacteriology and immunology. Nor should we neglect to be something even more important—adequate internists with perhaps some subsidiary competence such as in hematology. We come then to a citation of several examples out of the large number of roads to carry us over the horizon.

HISTOLOGY AND HISTOPATHOLOGY

To many of us, about 10 years ago, it seemed classical pathology and histopathology had become exhausted of any real hope for further yields. It had become a sterile "dead-house". Mere morphology as a pursuit was no longer interesting and failed to stir the more imaginative. But all this has suddenly changed to where morphology in a renaissance fired by newer techniques appears again to be at the center of our stage. What with the now pregnant histochemistry, with its staining of enzymes and proteins, the newer fixatives, such as the freezing-drying technique to preserve unchanged the details of the living, the immense resolution of the electron microscope and the probing with submicroscopic methods, morphology again assumes its earlier importance. We realize now the "H & E" method showed us only skeletons; yet dying suns in their agony are capable of blinding flashes. Thus the "L.E. cell", of such immense importance, is a gift of latter-day morphologists.

Without abandoning the classical methods, what are a few of the newer ones apt to reward with advances. In the field of study of cells, the polarization optical method holds great promise.

POLARIZATION OPTICS

Colloids do not refract polarized light but propagate it at the same velocity. Furthermore, they become birefringent if their particles are rod or plate-like and non-spherical. When drawn out or stretched or put under tension or pressure, they have the same action on polarized light. We can utilize these properties to recognize structural, intrinsic and strain refringence of such materials. Thus, oriented, optically isotropic, rod-shaped particles with one dimension small compared to the wave length of light are apt to exhibit structural birefringence. Optical anisotropy of individual particles brings forth intrinsic birefringence, in contrast to structural birefringence. High rates of shear in elastic gels and some liquids develop strain birefringence. By these means polarization studies can help us discern submicroscopic structure especially of materials with molecules of directed fibrous structure displaying double refraction.

Various investigators studying collagen, elastin and keratin as fibrous and related substances by these submicroscopic methods report slightly different results, though they all agree there are repetitive units forming chains, spirals, globules and other configurations. Workers are busy exploring the characteristics of these geometrical figures and how physical and chemical factors modify them reversibly and irreversibly. The dermatologic investigator of the future must

occupy himself seriously with such studies to yield fundamental information to define the ultimate details of some of the cutaneous diseases.

BIOLOGICAL ANTAGONISTS

Research workers are studying with considerable success and finding use in many fields of medicine for a newer principle, biological antagonism. It came into focus accidentally when they undertook to explain the action of the sulfonamides. This class of drugs, as well as other synthetic and naturally occurring ones,—biological antagonists—they said, have the ability to interfere with the action of a nutrient or physiologically essential constituent. Such blocking action depends on competition for the latter's enzyme of utilization or for the site of the action in or on a cell.

There are now a large number of synthetic antagonists against essential metabolites, for the vitamins and amino acids as well as for acetylcholine, epinephrine and some other hormones. There is a large number of synthetic analogues of essential amino acids, but only some are antagonists. An excess of one may interfere with renal absorption of another. Thus, glycine may interfere with complete reabsorption of creatin and produce a false creatinuria. Could this be a factor in dermatomyositis? Ethionine competes with methionine to bring about pathological states, such as kwashiorkor with its peculiar, red skin changes. There are analogues for tryptophane (of interest in pellagra), lysine, histidine, arginine (there is a plentiful supply of arginase in the skin and arginine in sweat), and tyrosine. The latter interests us with its possibilities for pigment study. Besides those for p-amino-benzoic acid and folic acid, there are antagonists for other members of the B-complex. There are reports that pantothenic acid has favorable local action against some dermatoses. Antagonists against this vitamin could help to explain how it works on the skin.

In recent years the study and use of histamine antagonists became commonplace. Only the synthetically prepared ones proved of practical value. Analogs of acetylcholine either antagonize or reinforce depending on whether they compete for the effective receptor site or an enzyme whose natural function is to destroy this chemical mediator. There would seem to be a rich harvest here awaiting the reapers.

Chelation is the process whereby organic acids form complexes with inorganic ions, removing the latter from their normal roles. Such action takes place, for example, when citrate removes calcium to prevent the clotting of blood. Many enzymatic reactions require the presence of traces of metallic ions, such as iron, copper, manganese, zinc and cobalt. Thus, 8-hydroxyquinoline is fungicidal, but the addition of zinc can overcome this action. Chelation is in the general class of biological antagonists, though without using analogues of metabolites, and is probably the basis of some of our older remedies used on the skin.

Many other biological antagonists exist now such as against thyroxine, morphine and the purines. The field is new (though Ehrlich thought of it more than fifty years ago), the number of agents studied numerous, and the skin would seem

to be the most convenient site to do this. Unquestionably, dermatologists of the future should make rich strikes there.

MUCOPOLYSACCHARIDES

It is over twenty years ago that Duran Reynals reported that testicular extract promotes the diffusion of virus and of particulate matter in the skin. This seemingly innocent observation was to have the most far reaching repercussions; not only in the realm of bacterial and viral invasiveness, but also in that of enzymology, for a new class of enzymes was thereby revealed: the mucinases. Further, a study of the substrates of these enzymes led to notable advances in the chemistry of the mucopolysaccharides, and of their breakdown products.

One component of the testicular extract, the spreading factor as it was first named, is now generally known by the name hyaluronidase; a mucolytic enzyme whose action it is to depolymerize, and then to break down chemically the substance hyaluronic acid. This had already been recognized as a component of the mesenchyme, along with chondroitin sulphuric acid, which is also broken down by the enzyme. Both hyaluronic acid and chondroitin sulphuric acid occur in human skin.

It was in the skin that the spreading reaction was first demonstrated, and in skin, or its appendages, some of the most striking physiological effects of modification of the ground substance and basement membranes may be noticed. Following wounding there appear rapid, profound alterations in the stainability and solubility of the ground substance, with loss of basement membranes. The connective tissue appears to become mobilized; the area becomes more fluid and less resistant, providing, presumably, favorable conditions for the ingress of cells and blood vessel sprouts. Similar changes are seen in the vicinity of vigorously growing subcutaneously implanted tumors. Instead of the normal tough resistant subcutaneous connective tissue, the connective tissue in the vicinity of the tumor is soft and jelly-like and can be cut with a blunt probe. The ground substance is more soluble, basement membranes thinned or absent. Conditions are favorable for tumor invasion of the connective tissue.

An implicit control of connective tissue by hormones has long been recognized. Recent experiments have shown that, under such control, changes in carbohydrate complexes may play a significant and perhaps dominant role. Referring again to work principally on the skin or its appendages, the following have been shown: In the higher primates the skin of the genital region—the so-called sex skin—swells and deflates with the menstrual cycle, and can be artificially stimulated by estrogen. Histochemical studies of swollen tissues reveals loss of glycoprotein, thinning of the basement membranes and water uptake. Parallel electrochemical studies show a parallel fall in the density of negatively charged colloids of the tissue. Similar observations were made on skin after the administration of cortisone, and on capons comb, after male sex hormone. The swelling seen in these tissues following hormone treatment is interpreted now as a relative increase of water soluble as compared with water insoluble colloids of the tissue, with a com-

pensatory uptake of water to maintain osmotic equilibrium. An important component of the colloid involved is the carbohydrate-containing mucopolysaccharides and mucoproteins of the tissues, whose behavior thus falls under hormonal control. New Methods—intravital staining, freeze-drying fixation of tissues with special staining, use of buffers and enzymes on sections, etc.,—have been used to investigate these changes in the ground substance of connective tissue. It would appear that a wide field for the investigation of many dermatological lesions is now available.

METABOLISM OF INTERMEDIATES

From various approaches there are aggressive and intense studies of the metabolism and biochemistry of intermediates to help understand the processes of cells and their environments, and the degradation and incorporation of foods. Earlier workers labeled dietary components by substituting for natural analogues in the diet, but this was only partially successful, because the labels employed changed the properties of the substance. It was from such attempts they deduced that the oxidation of fatty acids proceeds by the removal of two carbon atoms at a time.

The atomic age provided investigators with new tools in the artificially created stable and radioactive isotopes of practically every element. The isotope technique consists in using components containing atoms of abnormal isotope concentration. In this way one can detect the substance and estimate it quantitatively in the presence of its normal analogues and other compounds, while it behaves like its normal analogues in a biochemical system. Thus by this means one can detect the conversion of one compound to another, study the mechanism of biochemical reactions, measure rates of reaction and determine the amount of a constituent in a mixture. This method has the advantage of use in the intact animal under normal physiological conditions.

One of the earliest important results of the isotope technique was to discover the highly dynamic state of all tissue constituents. Thus even bone is found not to be static in its makeup, and the silent structures of liver and skin are seen to undergo intense and rapid change.

Investigators knew from feeding experiments with immature rats, phenylalanine is an essential part of the diet but tyrosine is not. These two amino acids have a chemical similarity making one suspect tyrosine is an oxydation product of the other. Some support for this suspicion comes from the common excretion product, p-hydroxyphenylpyruvic acid in tyrosinosis with the feeding of either one or the other of the above amino acids. For various reasons this evidence is not definitive, but by feeding rats a small amount of phenylalanine labeled with deuterium, one finds tyrosine in the tissues to contain a high concentration of deuterium. The conversion of phenylalanine to tyrosine is independent of the diet composition and there was no way to detect this fact before the use of isotope technique. For the student of cutaneous physiology and biochemistry such added knowledge of tyrosine reactions has significance.

The use of isotopes proved that part of the glycine molecule, the amidine group in arginine, and the methyl group in methionine went to make-up creatine. This could possibly be of use to some investigator studying the pathogenesis of dermatomyositis. Isotopes show tissue materials are not alone in their state of dynamic equilibrium, but share this state with the antibodies. Antibody protein breaks down and is continually being synthesized even when the antibody titer is declining. The feeding of isotopic glycine to an actively immunized rabbit even at the stage of falling titer results in rapid incorporation of the isotopic nitrogen within the antibody. The use of isotopes for investigation of problems in the physiology and diseases of the skin undoubtedly will accelerate since this organ by its accessibility lends itself to such use more than that of any other "fixed" tissue.

Many other interesting avenues await the enterprising investigator seeking to explore the cutaneous terrain. Some will want to search by way of mesomerism or viscometry, enzymology and hormones, histo- and immunochemistry and numerous other revealing pathways. Our future looms up more and more an exciting adventure and we can only envy those who follow us, fortunate enough to seek and find these roadways to the citadels of future dermatology.